Extremely Resistant Hyperthyroidism

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GRAVES' DISEASE is relatively uncommon in children. Hayles and coworkers[5] reported a total of 253 cases in patients less than 15 years of age at the Mayo Clinic in the 48 years 1908-1955. The ratio of females to males was 6:1. The cause of this disease is still unknown. Sometimes a long-acting thyroid stimulator (LATS) can be found in the blood. Factors influencing resistance to therapy are not well understood. This report deals with an extremely resistant case in a young patient.

Report of a Case

An 11-year-old Chinese girl was first admitted to Presbyterian Medical Center on November 8, 1961, with complaint of loss of weight, irritability, excitability and excessive perspiration.

On examination she was hyperactive but there was no exophthalmos. The thyroid gland was slightly enlarged. The blood pressure was 140/80 mm of mercury and the pulse rate was 140. Protein-bound iodine was 9.8 micrograms per 100 ml of blood (normal 3.6-7.6). Red cell uptake of T^3 triiodothyronine was 59 per cent (normal 13-20 per cent).

Propylthiouracil, 100 mg four times a day, was prescribed and the patient was dismissed from the hospital.

At first there was considerable clinical improvement and the red cell uptake of T^3 dropped to 21 per cent (Chart 1), but soon the symptoms began to recur and the amount of propylthiouracil was gradually increased to 800 mg a day with no significant clinical improvement. The T^3 uptake remained about 30 per cent.

On March 6, 1961, the patient was readmitted to the hospital and phenobarbital, 32 mg four times a day was given for sedation. The results of a radioiodine uptake study, done while the patient was

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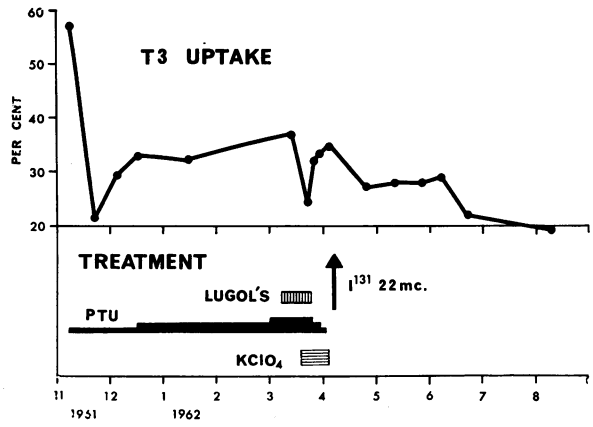

Chart 1.—Changes in the red cell uptake of triiodothyronine (T^3) during treatment. (Normal range 13 to 20 per cent.) Four months after the patient received a large dose of radioactive iodine, the result of the test was within normal range for the first time. (PTU = propylthiouracil; $KClO_4$ = potassium perchlorate.)

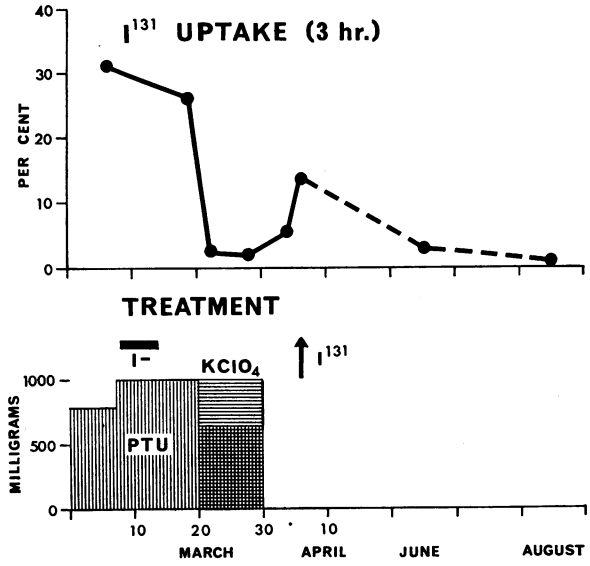

Chart 2.—Changes in the 3-hour uptake of I^{131} during treatment. (Normal range 5 to 15 per cent.) Large doses of propylthiouracil did not effectively block uptake. Perchlorate did block uptake but failed to affect the clinical hyperthyroidism. Note rapid rise in uptake after discontinuance of drugs. (I^- = iodide; $KClO_4$ = potassium perchlorate; PTU = propylthiouracil.)

taking 200 mg of propylthiouracil every six hours, was as follows: at one hour 28 per cent, three hours 31 per cent, five hours 33 per cent, 24 hours 22 per cent. The dosage of propylthiouracil was increased to 300 mg every six hours with no clinical or laboratory improvement. Lugol's solution, five drops four times a day, was given for one week, again with no improvement. Lugol's solution was discontinued and the patient was treated with potassium perchlorate, 250 mg every six hours, as well as propylthiouracil, 150 mg every six hours. Under this

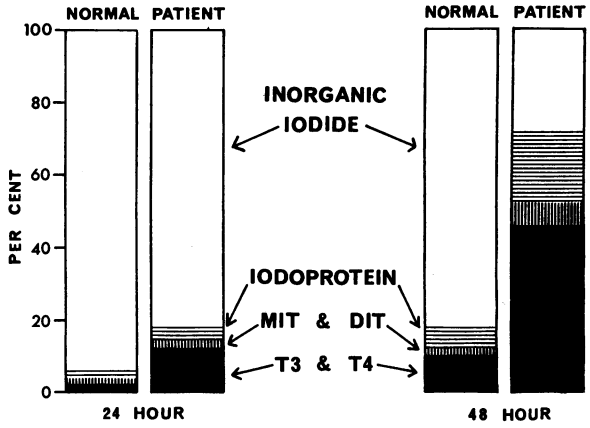

Chart 3.—Chromatographic analysis of iodinated compounds in the serum 24 and 48 hours after the therapeutic dose of I^{131} showed increased production of thyroid hormones—thyroxin (T^4) and triiodothyronine (T^3)—as compared to normal. MIT = monoiodotyrosine. DIT = diiodotyrosine.

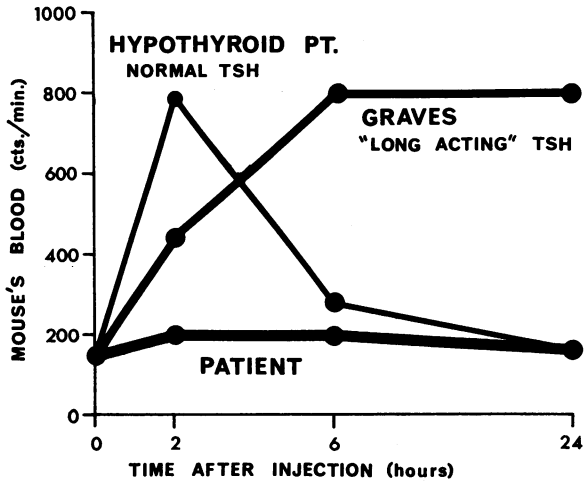

Chart 4.—Mouse assay for thyroid stimulating hormone consists of measuring release of radioiodine from the mouse's thyroid gland into his blood after intraperitoneal injection of human serum. Normal TSH (taken from a hypothyroid patient) gives a peak response at 2 hours. The serum of some patients with Graves' disease gives a prolonged effect lasting 24 hours or more. The patient's serum contained neither normal nor long-acting TSH. (TSH = thyroid stimulating hormone.)

regimen her three-hour uptake of I^{131} dropped to 2.5 per cent but over a period of ten days there was no clinical improvement and the red cell uptake of T^3 was consistently about 33 per cent. It was therefore decided that it would not be feasible to prepare this patient for surgical thyroidectomy and all antithyroid drugs were discontinued. The I^{131} uptake rose very rapidly (Chart 2) and three days later she was given a therapeutic dose of 20 millicuries of I^{131}. After this, she slowly improved but for almost three months remained clinically hyperthyroid and continued having greater than normal red cell uptake of T^3 (Chart 1). Subsequently, however, she became completely euthyroid, gained considerable weight, had red cell T^3 uptake of 17 per cent and three-hour I^{131} uptake of 6 per cent. The thyroid gland was no longer palpable.

Some special studies were done on the patient while she was in the hyperthyroid state: (a) ion exchange resin column chromatography of iodide compounds in her blood (Chart 3). Following administration of radioactive iodine she showed excessive production of thyronines (thyroxin and triiodothyronine) which is characteristic of Graves' disease.[2] (b) Bioassay for thyroid stimulating hormone and long-acting thyroid stimulator by the McKenzie mouse assay technique.[7] Despite the severe clinical course in this case, there was no detectable level of thyroid stimulating substance in the serum.

Discussion

The features of the case here reported bring into focus many of the current problems regarding our understanding of hyperthyroidism. We do not know the cause of the disease or why some patients are resistant to therapy. The author has reported on identical twins with hyperthyroidism; one of them considerably more difficult to treat than the other.[6] In the present case the disease resisted all forms of therapy: iodide, propylthiouracil, perchlorate and ultimately radioactive iodine.

Perchlorate blocks iodine uptake in the thyroid gland by competing with iodide for "trapping sites" on the thyroid cell. Hence it can be used in conjunction with the thiouracil drugs, which block the next step in thyroid hormone metabolism, namely the conversion of trapped iodide to iodine, but it cannot be used in conjunction with iodide (saturated solution of potassium iodide or Lugol's solution) because large quantities of iodide will displace perchlorate and break through the block. This material has been widely used as an antithyroid drug in England[2] but has found little favor in this country.

In general one prefers not to treat children or adolescents with radioiodine, although in fact there is no clear-cut evidence that such treatment increases the incidence of thyroid carcinoma. However, Sheline and coworkers[8] reported increased incidence of thyroid nodules several years after I^{131} treatment in a small group of children, and it is known that roentgen ray treatment to the neck region in infancy—and, to a lesser extent in adolescence—is associated with an increased incidence of thyroid carcinoma in later life.[3] For this reason we felt that in the present case it would be best to give a large obliterative dose of radioiodine so that there would be no thyroid tissue left to develop

neoplastic changes. Despite the large dose used, the patient had a significant amount of residual thyroid function long after treatment. When Adams[1] first described the abnormal long-acting thyroid stimulator (LATS) of Graves' disease, it was hoped that this substance could be incriminated as the specific cause of this disorder. Unfortunately, in most series, less than half the patients with Graves' disease have a detectable level by mouse bioassay. The source of LATS has not been determined. There is considerable evidence that it does not originate in the anterior pituitary gland.[9]

Summary

In an extremely resistant case of hyperthyroidism occurring in an 11-year-old Chinese girl, large doses of propylthiouracil and potassium perchlorate failed to control the disease and ultimately radioactive iodine was used. No significant level of thyroid stimulating hormone or long-acting thyroid stimulator could be detected in the blood of the patient.

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Multiple Cardiac Arrest

Two Cases Salvaged by Massage and Defibrillation, One Internal, One External

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THE FOLLOWING two cases are reported in order to illustrate the enormous change that has come about in the management of cardiac arrest in the last few years.

These two cases, which are comparable in many respects, represent catastrophic clinical events separated in time by four years. The first was managed by open chest cardiac massage and direct epicardial counter-shock defibrillation, the second by external cardiac massage and external defibrillation. In both cases the patient lived, but the second was far less traumatic to the patient and staff than the first.

Reports of Cases

CASE 1. A 58-year-old attorney was transferred to U.C.L.A. Medical Center from another hospital on January 4, 1958. Six days before, he had had a fainting episode in his home. His family physician who saw him shortly thereafter found him to have recovered, but counted a pulse of 40 beats per minute. Reasoning that he had complete heart block with Adams-Stokes attacks, the physician sent him by ambulance to the nearest hospital. During the trip the patient again lost consciousness and on arrival at the hospital appeared moribund: he was rigid and cyanotic and there was no perceptible pulse, blood pressure or respiration. Without hesita-